Childhood-Onset Schizophrenia: An NIMH Study in Progress

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Abstract

An ongoing study of the phenomenology, genetics, neuropsychology, physiology (eye tracking, autonomic responsivity), neuroimaging, biochemistry, and pharmacology of childhood-onset schizophrenia is described, and pilot data are presented for the first 22 subjects. Differentiation from autism "spectrum" disorders and other poorly defined, severe neurodevelopmental disorders is needed. Eye tracking and autonomic results are similar to patterns seen in later-onset schizophrenia and possibly more striking. Magnetic resonance imaging showed larger left frontal ventricular horn area for the schizophrenia subjects, larger left caudate, and lack of normal caudate asymmetry. Fluorodeoxyglucose positron emission tomography during an auditory continuous performance task revealed decreased right parietal/occipital glucose metabolic rate in the schizophrenia subjects, which may be secondary to poor attentional performance, and increased glucose metabolic rate in three left frontal regions, a left parietal region, and the right putamen. Clozapine has been effective and well tolerated in an open trial with 12 adolescents who responded poorly to typical neuroleptics; 16 subjects have been enrolled in a double-blind comparison of haloperidol and clozapine. Longitudinal study of this narrowly defined and possibly more homogeneous group of very early-onset schizophrenia subjects will be relevant to current neurodevelopmental theories addressing the role of puberty, progression of pathology, and continuity or discontinuity with later-onset schizophrenia.

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Schizophrenia, as defined in *DSM–III* (American Psychiatric Association 1980) has been described in children as young as 5 years (Green et al. 1984, 1992). However, little systematic research has focused on childhood-onset schizophrenia. The major impediment is not so much the rarity of the disorder—thought to be one-fiftieth the prevalence of the adult disorder (Beitchman 1985)—as sample heterogeneity. Previous broad or unspecified criteria for "childhood schizophrenia" grouped together subjects with autism, schizophrenia, organic mental disorders, borderline disorders, and probably major affective disorders (Prior and Werry 1986).

Schizophrenia in adults is almost certainly a heterogeneous disorder, with both genetic and environmental factors playing etiologic roles. Variability in age at onset has been noted since the earliest descriptions of the illness (Bleuler 1911/1950; Kraepelin 1919/1921), but nothing is known about the cause of this variability. Further, no data confirm or refute etiologic continuity of childhood-onset and later-onset schizophrenia.

The National Institute of Mental Health (NIMH) study of childhood-onset schizophrenia addresses the biological correlates of early onset and the question of continuity with later-onset disorder. If there is etiological continuity, then sys-

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tematic study of the childhood-onset subgroup may reveal more marked and consistent findings than adult studies, since earlier onset might result from a "heavier" genetic load or a more potent environmental insult. Increased familiality is observed in early-onset cases of a variety of diseases of multifactorial origin (Childs and Scriver 1986) and also has been observed in males who have schizophrenia with onset of psychosis before age 17 (Pulver et al. 1990). If childhood-onset cases have an even higher rate of familiality than those with adolescent onset, genetic studies should be particularly revealing in the childhood-onset group. Alternatively, earlier onset of illness may reflect a more salient environmental insult (e.g., intrauterine viral infection), premature endocrine influence on brain development, fewer protective factors, or greater psychosocial stress. In general, genetic and environmental insults would likely result in more consistent neurobiological findings in a childhood-onset group for whom there is less confounding by institutionalization, chronic neuroleptic treatment, and drug and alcohol abuse when compared with adult patients.

Since Kolvin's work in the early 1970s (Kolvin et al. 1971), autism and childhood-onset schizophrenia have generally been considered separate disorders. However, controversy continues over possible overlap, with reports of a high frequency of autistic symptoms in childhood-onset schizophrenia (Watkins et al. 1988), negative symptoms of schizophrenia in both disorders (Rumsey et al. 1985*b*, 1986) and, albeit rarely, children with autism diagnosed with schizophrenia as adults (Petty et al. 1984). Schizophrenia patients with pathophysiology similar to subjects with autism would presumably be overrepresented in cases with childhood onset, and neurobiological comparisons of such subjects with subjects who have autism would be enlightening.

This article reports pilot data from an NIMH study of childhood-onset schizophrenia examining phenomenology, neurobiology, and drug treatment. Data are presented for phenomenology, family history and chromosome analyses, smooth pursuit eye movements, autonomic physiology, magnetic resonance imaging (MRI), positron emission tomography (PET), and response to typical (haloperidol) and atypical neuroleptics. Although preliminary, these are some of the first neurobiological and pharmacological data available for well-diagnosed childhood-onset schizophrenia subjects.

Phenomenology

The few studies that have examined the phenomenology of childhood-onset schizophrenia by *DSM–III* criteria (Green et al. 1984, 1992; Russell et al. 1989) indicate that symptomatology and other diagnostic features are similar enough to those in adults that there is no justification for separate diagnostic criteria. Thus, in *DSM–III–R* (American Psychiatric Association 1987), identical criteria were used for diagnosis, no matter what the age at onset, and this practice continues in *DSM–IV* (American Psychiatric Association 1994).

Childhood-onset schizophrenia must be differentiated from an array of severe child psychiatric disorders with overlapping symptomatology. Social impairments, oddities of verbal and nonverbal communication, unusual perceptual experiences, and peculiar fantasies are characteristic of children with mild autism (Rumsey et al. 1986), Asperger's syndrome, and schizoid/schizotypal personality disorders in childhood (Kay and Kolvin 1987; Szatmari et al. 1989; McKenna et al. 1994*a*, 1994*b*). Also included in the differential diagnosis of psychosis in childhood are affective disorders with psychotic features (Chambers et al. 1982), multiple personality disorder (Malenbaum and Russell 1987), and severe obsessive-compulsive disorder (Hermesh et al. 1989). In addition, it is our experience that developmental expressive language disorder is sometimes misdiagnosed as thought disorder and interpreted as a psychotic symptom.

Over the past 5 years NIMH, through the American Academy of Child and Adolescent Psychiatry and the National Alliance for the Mentally Ill, has nationally recruited 6- to 18-year-old subjects meeting *DSM–III–R* criteria for schizophrenia with onset of psychosis before age 12. As of June 1994, medical records had been reviewed for more than 350 patients, and 98 patients and their parents had been screened in person. Patients were chosen for in-person screening if they met the above criteria, had an IQ above 70, and had no medical or neurological problems apparent from medical records and telephone interviews with parents and treating physicians. Travel and lodging expenses were paid by NIMH for those who could not afford them.

Consensus best-estimate primary diagnosis of the patients seen in person was made by two child psychiatrists on the basis of medical records, information from referring physician, and unstructured and structured interviews of the

child alone and parents alone. The structured interview consisted of portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version (Orvaschell and Puig-Antich 1987; Ambrosini et al. 1989) and the Diagnostic Interview for Children and Adolescents–Revised (Herjanic and Campbell 1977; Welner et al. 1987). The interview covered all major areas of psychopathology in childhood and adolescence.

Table 1 shows the consensus best-estimate primary diagnoses of the first 98 patients screened for the study. Using a narrow definition of schizophrenia in an effort to increase diagnostic homogeneity, we diagnosed 28 of these 98 patients with schizophrenia. Most disorders were anticipated, with the exception of a group of 21 patients who at first glance met *DSM–III–R* criteria for schizophrenia and whom other investigators might have so diagnosed. But this group of patients had a clinical presentation that differed from schizophrenia in affective and social impairments as well as the frequency and type of psychotic symptoms. No *DSM–III–R* diagnosis adequately describes this group of patients, and we have called them "multidimensionally impaired" (MDI). This diagnosis indicates that these children have multiple impairments in many areas of cognitive functioning but they differ from children with pervasive developmental disorders in their play interests and in their affective, social, and motor impairments (McKenna et al. 1994*a*, 1994*b*). The *DSM–IV* definition of borderline personality disorder comes closest to describing this group (American Psychiatric Association 1994).

MDI children from an early age exhibit marked affective instability and recurrent inappropriate outbursts of aggression or rage. Their relationships with adults are immature, overdependent, or clingy, and with peers they exhibit markedly impaired social judgment, which often results in their being teased or scapegoated. They very much desire social contact but are inept. Their thinking is immature, and fantasy and reality may appear to merge—they live in a "cartoon world." Suspiciousness and ideas of reference are common, but firmly held, systematized, or bizarre false beliefs are absent. Perceptual aberrations—such as excessive hypnogogic and hypnopompic hallucinations, illusions, or fleeting hallucinations with stress—are common, but there are no persistent hallucinations in the absence of severe, acute stress. There is no formal thought disorder as in schizophrenia, but developmental language disorders are common and may result in speech that appears "disjointed," particularly when the patient is anxious. Specific developmental disorders and attention deficit hyperactivity disorder are nearly always comorbid. Symptoms are severe and usually date to the preschool years; first contact with mental health professionals is usually at age 6 or earlier and hospitalization usually occurs by age 8. The MDI group has been reliably diagnosed using empirically derived criteria (kappa of 0.81 with two child psychiatrists independently diagnosing 53 psychotic patients) and will serve as an important contrast group for the childhood-onset schizophrenia subjects in neurobiological studies.

Clinical characteristics of the 22 schizophrenia subjects (14 male, 8 female) enrolled as of July 1994 (from 98 patients screened in person) are shown in table 2. Of the children screened, those given the diagnosis of schizophrenia ranged in age from 10 to 18. At the time of the study, only one subject was prepubertal, and retrospective as-

Table 1. Best estimate primary diagnosis of first 98 subjects screened for childhood-onset schizophrenia study (as of August 1994)

Diagnosis	*n*
Schizophrenia	28
Multidimensionally impaired	21
Bipolar disorder	11
Major depression	8
Asperger's syndrome/pervasive developmental disorder NOS	7
Schizotypal personality disorder	4
Attention-deficit hyperactivity disorder/conduct disorder/oppositional defiant disorder	7
Dissociative disorder, NOS/PTSD	4
Obsessive compulsive disorder	2
Schizoaffective disorder	2
Organic psychosis	3
Tourette's syndrome	1

Note.—NOS = not otherwise specified; PTSD = posttraumatic stress disorder.

Table 2. Clinical characteristics of subjects in NIMH childhood-onset schizophrenia study (n = 22)

Measure	Mean (SD)	Range
Sex:		
Female: 8	—	—
Male: 14	—	—
Type:		
Subacute: 8	—	—
Insidious: 14	—	—
Age (yrs) seen at NIH	14.4 (2.0)	10–18
Age (yrs) at onset of psychosis	10.4 (1.3)	7–12
Neuroleptic exposure (mo)	22.0 (15.2)	2–54
Hospitalization (mo)	7.8 (10.2)	0–37

Note.—NIMH = National Institute of Mental Health; NIH = National Institutes of Health; SD = standard deviation.

sessment showed that the other subjects were prepubertal or in early puberty (Tanner stage II) at the onset of psychosis (all but 3 had onset between 9–12). Onset was subacute (deterioration from baseline to psychosis = 1–6 months) in 8 subjects and insidious (deterioration over more than 6 months) in 14. Despite their young age, the group was relatively chronic, with significant neuroleptic exposure.

Surprisingly, the distinction between positive and negative symptoms has not been systematically examined for childhood-onset schizophrenia, in which negative symptomatology is less confounded by secondary negative symptoms from chronicity of illness, long-term institutionalization, and chronic drug treatment. All 22 subjects had severe and persistent delusions and/or hallucinations, and all but 1 subject had formal thought disorder. Negative symptoms such as flat affect, alogia, apathy, asociality, and inattention were also common, however, and severe as measured by the Schedule for the Assessment of Negative Symptoms (Andreasen 1982).

Family History and Chromosome Analysis. First-degree relatives of the 23 schizophrenia probands underwent nonblind structured interviews by an experienced clinician using the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott 1978); 3 of the families (13.6%) had first-degree relatives with nonaffective psychotic disorders. In one family, the mother was diagnosed with delusional disorder and there were also nonaffective psychotic diagnoses in the maternal uncle, grandfather, grandmother, and great-aunt but none on the paternal side. In the second family, the mother had schizoid disorder with a history of multiple episodes of hallucinations requiring treatment, several siblings had schizoid or schizotypal disorders, and one sibling had schizophrenia. In the third case, the child's father had a history of nonaffective psychotic disorder. While greater familiality was hypothesized for childhood-onset cases, a larger sample will of course be needed to address this issue. Moreover, selection bias may be a factor in producing fewer familial cases, as it may take more adequate coping style to deal with the telephone contact and long distance travel that were necessary for participation in this study.

One of the 22 patients (a 12-year-old male) had an apparently balanced translocation involving chromosomes 1 and 7 (46,XY,t[1;7][p22;q22]) (Gordon et al. 1994) and a previously reported case of a 6-year-old boy with autism showed a complex chromosomal rearrangement involving the same chromosome 1 breakpoint (p22), chromosome 7 (different breakpoint), and chromosome 21 (Lopreiato and Wulfsberg 1992). Since chromosomal rearrangements may disrupt critical genes within the breakpoint regions, further study of the 1p22 region is warranted in developmental brain disorders.

Smooth Pursuit Eye Movement (SPEM)

Abnormalities in SPEM have been observed in 50 to 85 percent of adults with schizophrenia (compared with 8% of normals) even in remission (Iacono and Koenig 1983; Holzman 1989). SPEM dysfunction has been associated with negative symptoms (Sweeney et al. 1989) and lateral ventricular enlargement (Weinberger and Wyatt 1982), appears to be trait related, and cannot be attributed to typical neuroleptic use, inattention, poor motivation, or generalized deficits (Mather 1985; Smeraldi et al. 1987; Holzman 1989).

The developmental sequence for smooth pursuit tracking abilities, assessed by infrared oculography,

parallels that of other frontal lobe functions. Age is correlated with smooth pursuit system performance in 8- to 15-year-old subjects; this performance reaches adult levels by age 14 (Ross et al. 1993).

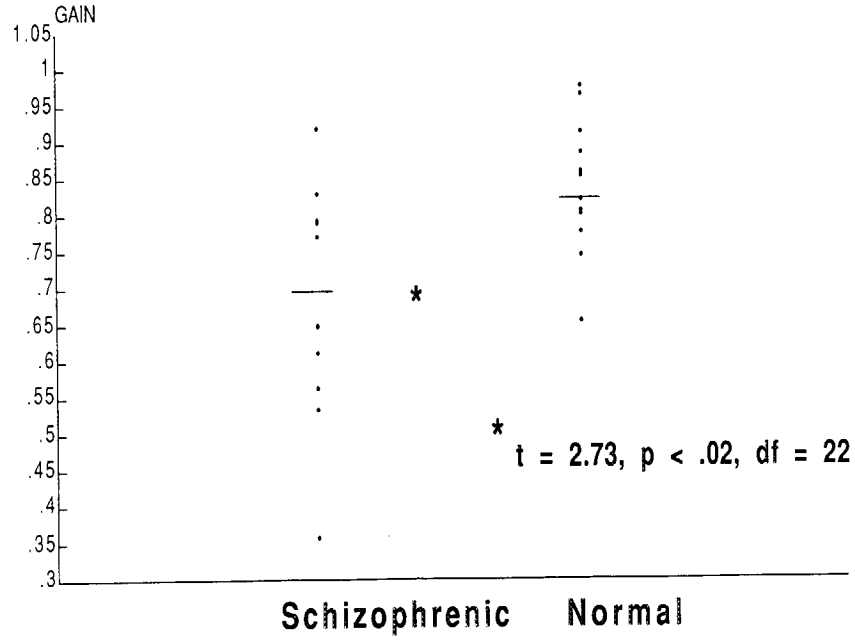
Eye movements have been measured in 10 childhood-onset schizophrenia patients (mean age = 14.9 years) and 12 normal control subjects (mean age = 12.8 years); 8 were on clozapine and 2 on haloperidol (figure 1). Intervals for smooth pursuit and saccadic eye movements were measured by high-resolution infrared oculography. Testing was technically difficult, and sometimes impossible, with medication-free subjects. Eye movements were analyzed only when it was clear that the subject was attempting to track the target. Performance was compared between groups with *t*-tests (two-tailed).

SPEM gain (eye velocity relative to target velocity) was significantly lower in schizophrenia subjects (0.69 ± 0.17) than in normal controls (0.84 ± 0.09) ($t = 2.7$, $df = 22$, $p < 0.01$). Furthermore, the distance covered (degrees per second) by total saccades, catchup saccades, and intrusive saccades was greater in the schizophrenia subjects (total: schizophrenia subjects 10.4 ± 7.9 vs. control subjects 4.0 ± 1.9 [$t = -2.8$, $df = 22$, $p < 0.01$]; catchup: schizophrenia subjects 3.7 ± 2.4 vs. control subjects 1.5 ± 0.8 [$t = -3.1$, $df = 22$, $p < 0.005$]; intrusive: schizophrenia subjects 5.1 ± 4.0 vs. control subjects 1.9 ± 1.0 [$t = -2.8$, $df = 22$, $p < 0.01$]).

The differences in SPEM gain between early-onset schizophrenia patients and controls might in part be secondary to clozapine treatment, which has been noted to adversely affect SPEM (Litman et al. 1994). But, compared with adult controls, the degree of impairment of SPEM in our childhood-onset schizophrenia patients is greater than that seen in adult patients treated with clozapine. Moreover, our childhood-onset patients made more intrusive saccades than the controls, whereas adult patients treated with clozapine do not show this dysfunction. It is unlikely that poorer tracking in schizophrenia patients can be explained by poor attention, since data were analyzed only if patients were clearly attempting to track the target. Moreover, a second age-matched contrast group of children with attention deficit hyperactivity has been tested and does not exhibit these eye tracking abnormalities (Dr. Daniel Hommer, personal communication 1994).

Poor SPEM gain and increased distance covered by saccadic movements found in these young schizophrenia subjects are similar to findings in adult schizophrenia patients (Radant and Hommer 1992) and are consistent with etiologic continuity between childhood-onset and later-onset forms of the illness.

Figure 1. Smooth pursuit gain in children with schizophrenia ($n = 11$) and normal children ($n = 13$)



Autonomic Responsivity

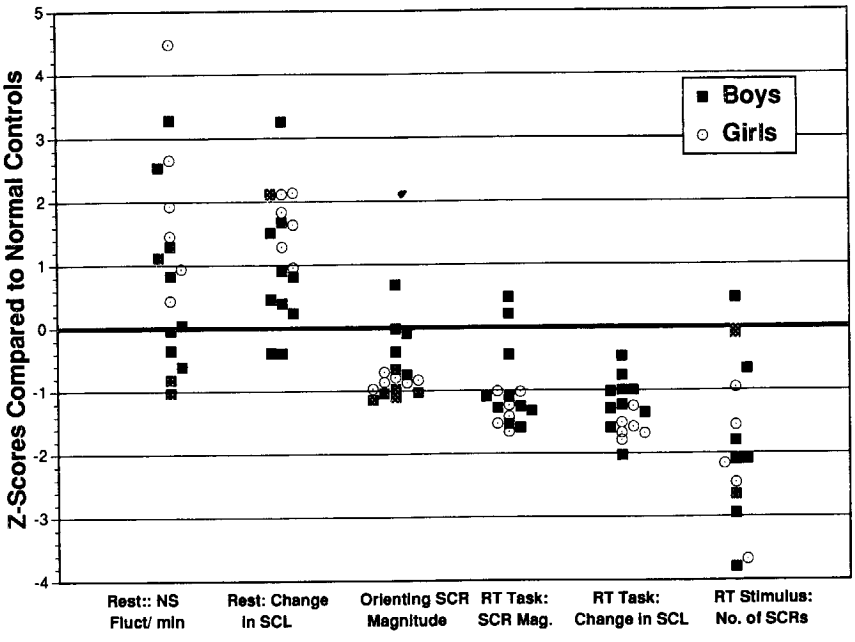
Electrodermal activity (EDA)—as indexed by skin conductance (SC)—and heart rate (HR) was assessed in a protocol that included a 3-minute rest period, a series of 10 nonsignal tones to elicit orienting responses, and a simple warned reaction time (RT) task. Eighteen schizophrenia patients (medication free for at least 3 weeks) were tested. SC level (SCL) could not be recorded for one patient. The RT task was not attempted with this patient, one

other, and two additional patients could not do the RT task. Thus, the *n*s ranged from 14 to 18 for different variables. The schizophrenia subjects are compared by 2-sample *t*-tests with a control group of 54 normal volunteers (35 male, 19 female) of the same age, except where noted. In addition, the scores for each patient on selected variables were converted to Z scores based on the normal mean and standard deviation for that sex group. The distributions of these Z scores for selected variables are plotted in figure 2.

Rest Period. Three indices of resting autonomic nervous system activity ("arousal") were examined. The rate of nonspecific fluctuations of SC in the rest and tones periods were higher in the patients ($p = 0.02$; figure 2), although SCL was not different from that of controls; HR was also elevated in the schizophrenia subjects ($p < 0.03$). SCL normally declines during the rest period and can be interpreted as a measure of adaptation to the situation. The rate of change in SC was less negative in the patients than in the controls ($p = 0.0001$; figure 2).

The results for all four of these variables (nonspecific fluctuations, SCL, HR, and change in SCL during the rest period) are very similar to what this laboratory has found in earlier studies of adult acute schizophrenia patients (Zahn et al. 1981*a*).

Figure 2. *Z* scores for the schizophrenia subjects for several variables based on the mean and standard deviations for age- and sex-matched normal controls (*n* = 53)



NS Fluct/min = number of nonspecific fluctuations of skin conductance per minute; SC = skin conductance; SCL = SC level; SCR = SC response; RT = reaction time; Mag. = magnitude.

Skin Conductance Orienting Response (SCOR). A SCOR was defined as an increase in conductance of a least 0.02 μS with an onset latency between 1 and 4 seconds. Over all trials, the patients gave fewer SCORs than controls ($p < 0.05$), but more importantly, 47 percent of the patients versus 2 percent of the controls failed to respond to the first tone ($p < 0.0001$, Fisher's exact test), and 35 percent of the patients versus none of the controls could be considered nonresponders on the basis of no SCORs on the first two trials ($p = 0.0001$). This marker is frequently found in about 50 percent of chronic patients (Zahn et al. 1991). The SCORs were consistently smaller in amplitude in the patients ($p = 0.0001$; figure 2) similar to our previous adult studies.

RT Task. In contrast to their high rate of nonspecific fluctuations in SCL during the rest period, patients had fewer such fluctuations in SCL than controls during instructions for the RT task ($p = 0.001$), and their magnitudes were smaller ($p = 0.0001$; figure 1). The increase in SCL during the RT instructions was markedly less for the patients than for the controls ($p < 0.0001$; figure 2). Patients were also autonomically less responsive than controls to the individual stimuli in the RT task. The number of skin conductance responses (SCRs) (figure 1) and their magnitudes were both much lower in the patients ($p < 0.005$). This pattern of findings is similar to previous reports for adult schizophrenia patients.

In summary, childhood-onset schizophrenia patients had high

baseline autonomic activity, slow adaptation and habituation, and impaired phasic and tonic autonomic responses to novel and significant stimuli and situations of the experimental protocol. The results are qualitatively similar to those obtained in adult schizophrenia patients in this laboratory (Zahn et al. 1981*a*) and elsewhere (reviewed in Zahn et al. 1991). However, the high degree of consistency on these markers shown by the present childhood-onset group is unusual in studies in adult schizophrenia. In this respect, they resemble more closely acute schizophrenia patients selected on the basis of a poor short-term outcome (Zahn et al. 1981*b*). The data thus suggest that in that sense they may be considered severely afflicted with the illness.

Finally, the findings have diagnostic specificity, since they contrast with results of studies using the same protocol on children with disruptive behavior disorders or obsessive-compulsive disorder (Berg et al. 1986; Zahn and Kruesi 1993) and adult men with autistic disorder (Zahn et al. 1987).

MRI. Both anatomic and functional developmental abnormalities have been proposed as etiological factors in later-onset schizophrenia (Weinberger 1987). Extension of these studies to pediatric samples will test some assumptions of these theories.

Ventriculomegaly has been reported in adults with schizophrenia in more than 90 computed tomography (CT) and MRI studies (Casanova et al. 1991) and may be associated with negative symptoms (Andreasen et al. 1990). Reduced volume of medial temporal lobe structures has also been found in multiple MRI studies (Suddath et al. 1989, 1990; Dauphinais et al. 1990), with gray rather than white matter accounting for the temporal lobe pathology (Suddath et al. 1989).

Several studies have demonstrated abnormalities in the corpus callosum in adult schizophrenia subjects (Nasrallah et al. 1986; Stratta et al. 1989; Casanova et al. 1990*b*; Swayze et al. 1990). Because the corpus callosum develops embryologically in association with limbic structures (hippocampal formation, fornix, hippocampal commissure, septum pellucidum, cingulate gyrus), which are also implicated in schizophrenia, callosal abnormalities support a neurodevelopmental basis of adult schizophrenia (Swayze et al. 1990).

To date, MRI has been carried out for 19 adolescent schizophrenia subjects and 37 normal controls matched for age, height, weight, Tanner stage, and handedness using a 1.5-tesla General Electric scanner (spoiled gradient recall acquisition at steady state, time to echo = 5 ms, time to repetition = 24 ms, flip angle = 45°) with 1.5 mm sagittal and 2 mm coronal contiguous slices. The volume of cortical (right and left total brain, frontal, prefrontal, and anterior, middle, and posterior temporal lobes) and 11 subcortical (right and left caudate, cingulate, hippocampus, and ventricular volume, total and subdivisions of the corpus callosum, midbrain, and pons) structures were measured (Giedd et al., submitted for publication).

Schizophrenia patients had an 8 percent smaller total brain volume and a trend for larger left ventricular volume (p = 0.09, two-tailed). In addition, they had significantly greater caudate volume particularly on the left. This is of considerable interest since the normal development across this age range is for a robust decrease in caudate volume (Castellanos et al., in press), suggesting that normal "pruning," programmed cell death, or other possible mechanisms may have failed to occur. The findings shown in table 3 have also been reported in adult schizophrenia patients. The pattern of abnormality, even with this incomplete analysis, already appears more pronounced

Table 3. Anatomic brain magnetic resonance imaging measures for subjects with childhood-onset schizophrenia (n = 19) and age-, sex-, and height-matched controls

	F[1]	p[2]	Adjusted means
Cortical			
Right occipital	4.04	0.04	N > S
Left occipital	7.39	0.009	N > S
Subcortical			
Left caudate	7.21	0.009	S > N
Splenium of corpus callosum (area)	3.38	0.07	S > N
Left ventricle	2.99	0.09	S > N

[1]Analysis of covariance with total brain volume (schizophrenia subjects total brain volume 8% less than normal volunteers).
[2]Two-tailed.

on the left.

The preliminary finding of enlarged left ventricular volume supports the hypothesis that ventricular enlargement is present early in the course of the illness and is consistent with asymmetric involvement (Crow 1990). However, ventricular enlargement does not seem more marked than for adult patients. These findings are not seen in age-matched subjects with attention deficit hyperactivity disorder and this suggests some specificity of these findings (Castellanos and Giedd, personal communication 1994). An interesting finding would be evidence for areas of *greater* developmental disruption than seen for later-onset disorder. A prospective followup MRI study is ongoing for all schizophrenia subjects.

Functional Neuroimaging

Functional brain imaging, such as PET and single photon emission computerized tomography (SPECT), is an important counterpart to anatomic investigations. Excess production of neurons, synapses, and dendritic spines early in development, and synaptic pruning and programmed cell death occurring throughout childhood and adolescence, parallel age-related changes in cerebral glucose metabolism. Metabolic rates rise until age 3 or 4, and these levels are maintained until age 9, followed by decline to adult levels by late adolescence (Chugani et al. 1987; Feinberg et al. 1990). PET studies of childhood-onset cases might be particularly illuminating; for example, such studies might indicate a different global rate of metabolism, suggesting an abnormal pattern of programmed cell death in early-onset schizophrenia (Feinberg 1982/83). In addition, any regional abnormalities in glucose metabolism in childhood-onset schizophrenia are of interest in relation to those seen in adult schizophrenia and autism.

Reduced frontal, temporal, and parietal metabolism have each been noted in [^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET studies of adult schizophrenia (Buchsbaum et al. 1982, 1984; Farkas et al. 1984; Wolkin et al. 1988; Cleghorn et al. 1989; Buchsbaum 1990). PET studies in adults with autism have not shown any localized abnormality (Rumsey et al. 1985*a*; Herold et al. 1988), although autism subjects showed fewer large positive correlations between cortical and subcortical regions (Horwitz et al. 1988), a finding that is consistent with mesolimbic dysfunction.

To date, 9 subjects with childhood-onset schizophrenia and 12 normal controls matched for age and sex have undergone FDG PET scanning. All subjects were medication free for at least 3 weeks. Subjects received 1.6–2.3 mCi (millicuries) of FDG intravenously. Eyes were closed and patched and subjects performed an auditory attention task through headphones throughout the period of glucose uptake. During this period, serial arterial or arterialized venous blood samples were taken from the arm for quantification of FDG uptake. After the uptake period, subjects were scanned for 30 minutes with a Scanditronix PET (ring or pin transmission scans). Slices were parallel to the canthomeatal line (CM), and the interslice interval was 5–6 mm. Whole brain and 60 regional measures of glucose metabolic rate were examined. For the extraction of regional glucose metabolic rates, boxes were placed over the regions of interest in five standard planes: planes A (9.1 cm above CM), B (7.8 cm above), C (6.5 cm above), D (5.2 cm above), and E (3.9 cm above).

Global glucose metabolism of subjects did not differ significantly from that of controls. With the data normalized to minimize the effects of individual variation in global metabolism on regional comparisons, schizophrenia subjects showed decreased metabolism in only one region: plane C right parietal ($p < 0.05$). Right parietal glucose metabolic rate was positively correlated with auditory continuous performance task performance (Cohen et al. 1987) in both schizophrenia subjects ($p = 0.06$) and normal controls ($p = 0.21$). When this region was reanalyzed, covarying for attentional performance, there was no difference between groups, indicating that metabolic differences were probably secondary to poor attention during the task for the schizophrenia subjects.

Increased glucose metabolism in the schizophrenia group was seen in four cortical regions and one subcortical region: plane E left inferior frontal ($p < 0.01$), plane B left parietal ($p < 0.01$), plane B left posterior frontal ($p < 0.05$), plane A left anterior frontal ($p < 0.05$), and right anterior putamen ($p < 0.05$). The lack of hypofrontality (and actual hyperfrontality in three regions on the left) in the childhood-onset cases is interesting, especially since Cohen et al. (1987) found hypofrontality in adult schizophrenia subjects by FDG PET using the identical vigilance task and region-of-interest analysis. Increased metabolism in the basal ganglia has been reported in adult schizophrenia subjects and is thought to reflect, at least in part, chronic neuroleptic administration

(Buchsbaum et al. 1987; Szechtman et al. 1988). We cannot reject this interpretation for our finding of increased metabolic rate in the putamen because our subjects, although young, had an average of 3 years of neuroleptic treatment. The right putamen metabolism did not, however, correlate significantly with duration of neuroleptic exposure.

These data are, of course, preliminary because of the small sample size. A larger sample, MRI-PET coregistration, and statistical pattern analyses of the relationships between metabolism in cortical and subcortical structures will allow better comparison with later-onset schizophrenia and autism.

Neurochemistry

No conclusions can be drawn from the few neurochemical studies of childhood-onset schizophrenia, especially given the drawbacks of small sample sizes and nonstandardized diagnostic criteria (Gillberg et al. 1983; Weizman et al. 1984; Rogeness et al. 1985). The serotonin system is of particular interest in our pediatric sample, since hyperserotonemia has been found consistently in 25 percent or more of patients with autism and at an increased rate in their family members (Anderson et al. 1987; Cook 1990). In the NIMH study, we are focusing on dopaminergic and serotonergic function so that we can contrast our results with studies of later-onset schizophrenia and autism. Cerebrospinal fluid, plasma, and 24-hour urine specimens are collected during a medication-free state, as well as during treatment with haloperidol and clozapine. These cerebrospinal fluid chemistries of children with schizophrenia will be compared with those of age-matched subjects with attention deficit disorder, conduct disorder, and obsessive-compulsive disorder, since it has not been possible to obtain spinal fluid from normal controls. On the basis of research in adult schizophrenia and autism studies of norepinephrine (Breier et al. 1990), neuropeptides (Weizman et al. 1984; Bissette et al. 1986), cyclic adenosine-3′:5′-monophosphate (Belmaker et al. 1984), nerve cell adhesion molecule serum fragment (Lyons et al. 1988; Plioplys et al. 1990), and epinephrine (Berger et al. 1984) are also being considered.

Treatment

Anecdotal reports have suggested that neuroleptic medication is less effective in children with schizophrenia than in patients with adult-onset illness (Kydd and Werry 1982; Campbell and Spencer 1988). Recently, the first controlled study of neuroleptics in children with schizophrenia has been carried out in 20 such subjects, ages 5–11 years (Spencer et al. 1991). Moderate improvement was seen in a variety of symptoms with haloperidol (0.5–3.5 mg/day) compared with placebo in a crossover design with 4 weeks on each treatment.

A single-blind comparison of thiothixene and thioridazine in 21 adolescents with schizophrenia found both neuroleptics equally effective in improving Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) scores, but the adolescents remained quite impaired (Realmuto et al. 1984). The only double-blind and placebo-controlled neuroleptic trial in adolescents with schizophrenia revealed only modest efficacy of loxapine and haloperidol (Pool et al. 1976); only two of the symptoms most important in schizophrenia showed a difference between drug and placebo after 4 weeks of treatment (BPRS hallucinations and disorientation).

Among the many neuroleptics available, haloperidol is the best studied for nonschizophrenic mental disorders of children and adolescents. Controlled studies have demonstrated safety and efficacy in the treatment of behavioral difficulties in infantile autism (LeVann 1969; Faretra et al. 1970; Engelhardt et al. 1973; Perry et al. 1989) and childhood-onset pervasive developmental disorder (Joshi et al. 1988), tics in Tourette's disorder (Feinberg and Carroll 1979; Bruun 1984), and undersocialized aggressive conduct disorder (Campbell et al. 1984). These results suggest that a positive clinical response is not diagnostic.

Recently, open studies and case reports of the use of clozapine in adolescents with schizophrenia who are considered unresponsive to or intolerant of typical neuroleptics suggest that the subjects improved in both positive and negative symptoms and that they tolerated the medication well (Siefen and Remschmidt 1986; Remschmidt 1991; Birmaher et al. 1992; Jacobsen et al. 1994; Mozes et al. 1994; Towbin et al. 1994). The NIMH study includes the first controlled trial of clozapine in children and adolescents with schizophrenia who are nonresponsive to typical neuroleptics.

Following a 4-week medication-free period, subjects in the NIMH study are randomized in a double-blind fashion to haloperidol plus benztropine or clozapine plus placebo. Dosages are increased twice weekly over the course of 6 weeks until positive effects, side

effects, or maximum doses (36 mg haloperidol or 900 mg clozapine) are achieved. At the end of 6 weeks, the blind is broken and those patients who received haloperidol may receive an open trial of clozapine if this is clinically indicated.

Sixteen patients have completed the double-blind trial to date, eight receiving clozapine and eight receiving haloperidol. However, because 4 subjects received open clozapine before the study began, a total of 12 adolescents have received open clozapine (mean week-6 dose, 366.7 mg/day); data on the first 11 have been reported previously (Frazier et al. 1994). One patient had concomitant digoxin for paroxysmal supraventricular tachycardia (diagnosed before initiation of clozapine) and another had concomitant valproic acid for suspected complex partial seizure disorder. The baseline BPRS total score for these 12 subjects was 86.3 (±13.2) and at week 6 of clozapine treatment was 53.5 (±20.6). These results are not surprising for such impaired, treatment-refractory patients receiving an experimental treatment. However, some patients have shown dramatic improvements. For instance, one patient, poorly responsive to multiple neuroleptics, including haloperidol, went from a catatonic state (mute, feces smearing) to being coherent, articulate, and free of psychotic symptoms within 3 months of clozapine treatment. Fifteen of the 20 patients completing the program thus far have remained on clozapine (longest followup is 2½ years). Side effects have been similar to those seen in adults, with the possible exception that weight gain may be more problematic in adolescents; mean weight gain for 12 patients in 6 weeks was 14.4 lbs, as opposed to 13.9 lbs in adults over a 16-week period (Leadbetter et al. 1992). Two patients experienced transient, benign neutropenia, but were able to remain on medication.

Clozapine therapy had to be terminated in 5 out of 20 patients completing the protocol thus far. Two of the five developed recurrent neutropenia despite medication interruption and rechallenge (absolute neutrophil counts between 1,100–1,500). Two patients experienced tonic-clonic seizures, and even with anticonvulsant therapy, were unable to tolerate clozapine due to ongoing cortical epileptiform activity. Finally, the fifth patient stopped clozapine therapy due to excessive weight gain.

Changes in blood, urine, and cerebrospinal fluid levels of monoamines and their metabolites during haloperidol (typical neuroleptic) treatment and clozapine (atypical neuroleptic) treatment will be compared and correlated with clinical response. Pharmacokinetics and plasma level monitoring of haloperidol and clozapine and their major metabolites are also being carried out to compare the pharmacokinetics in psychotic children and adolescents with data from adults (Piscitelli et al., in press).

In summary, data from our open treatment suggest that clozapine is possibly efficacious in 12 adolescents (mean age 14.1 ± 1.6) with childhood-onset schizophrenia who had been unresponsive to typical neuroleptics. Our double-blind comparison of the response of children with schizophrenia to haloperidol and clozapine along with a study of the phenomenology, neuropsychology, and biology of these children will better characterize the disorder. Given its efficacy against negative symptoms (Stephens 1990) and serotonin (5-HT_2) blocking activity (Wilmot and Szczepanik 1989), clozapine may be particularly beneficial in childhood-onset schizophrenia patients, since negative symptoms appear prominent and a relative hyperserotonemia is predicted for this subgroup.

Summary

Studies of the phenomenology, developmental course, and neuropsychological profile, as well as complementary genetic, neurobiological, and pharmacological response studies of childhood-onset schizophrenia are under way at NIMH. A number of developmental disorders may mimic childhood-onset schizophrenia, including two groups with disorders unique to child psychiatry: the MDI group and the pervasive developmental disorder/Asperger's syndrome group.

The 22 narrowly defined schizophrenia subjects (ages 12–18) enrolled to date in the NIMH study were severely ill with prominent positive and negative symptoms, had onset of psychosis between ages 7 and 12, and were prepubertal or in early puberty (Tanner II) at onset of psychosis (which was subacute or insidious); most had significant neuroleptic exposure. Pilot data from studies of SPEM and autonomic activity indicate continuity with later-onset schizophrenia. Preliminary quantitative MRI measurements showed larger left ventricular volume and smaller total brain volume. FDG PET showed decreased metabolism in a right parietal region, which is associated with poor attentional performance in individuals with schizophrenia, and increased me-

tabolism in three left frontal, a left parietal, and a right basal ganglia region. Clozapine has appeared efficacious in an open trial with 12 subjects, but its efficacy is yet to be established in an ongoing double-blind comparison with haloperidol.

To date, systematic study of the childhood-onset subgroup of schizophrenia subjects has not been actively pursued because of the rarity of the disorder and its diagnostic heterogeneity. However, the recent refinement of diagnostic classification, which began with *DSM–III*, together with recent advances in genetic methodology, brain imaging, and psychopharmacology, make such study timely.

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